

**Office Action Summary**

Applicati n N .

09/886,773

Applicant(s)

BEMIS ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 76,102-107,118 and 125-128 is/are pending in the application.
- 4a) Of the above claim(s) 105-107 and 118 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 102-104 and 125 is/are allowed.
- 6) ☒ Claim(s) 76 and 126-128 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

Pursuant to the directives of paper No. 7 (filed 4/2/03), claim 125 has been amended.

Applicants' arguments filed 4/2/03 have been considered and found persuasive. Claims 102-104 and 125 are now allowable. Claims 76 and 126-128 are now rejoined with the elected group. Claims 105-107 and 118 remain withdrawn from consideration.

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Claim 76 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 is indefinite as to what is encompassed by the term "IL-1 mediated disease". How directly must IL-1 be involved? If there is a biochemical process that is 20 steps removed from the main cause of the disease, and if that biochemical process leads, through a series of other steps, to a slight increase or decrease in IL-1, would such a disease be encompassed?

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 76 and 126-128 are rejected under 35 U.S.C. 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that some of the claimed compounds will inhibit interleukin-1- $\beta$  converting enzyme *in vitro*. Claim 126 is drawn to a method of promoting wound healing; claim 127 is drawn to a method of treating or preventing septic shock, septicemia, adult respiratory distress syndrome, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, or primary lateral sclerosis. However, there is no evidence that any of the claimed compounds can be used to promote wound healing or to treat any of the recited diseases.

Numerous hurdles remain to be overcome in making the transition from the test tube to the intact organism. Accordingly, the specification does not teach the skilled biochemist to use the claimed "pharmaceutical" compositions to successfully treat human disease.

It is noted preemptively that Ku (*Cytokine* 8, 377, 1996), discloses that there exist at least two compounds which inhibit "ICE", and which also show some benefit in a mouse model of type-II collagen-induced arthritis. However, this does not mean that other compounds

which also inhibit ICE to some degree will also be therapeutically effective. A key issue is that of relative efficacies at ICE inhibition. If the inhibitor efficacy of applicants' claimed compounds falls short of the efficacy of the "Ku" compounds, there is no reason to expect efficacy in treatment of arthritis, or any other disorder. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. One can look to applicants' own data in the specification for evidence of unpredictability in structure/activity relationships. [Additional data on structure/activity relationships can be found in the following: Dolle (*J. Med. Chem.* **39**, 2438, 1996); Dolle (*J. Med. Chem.* **40**, 1941, 1997); Dolle (*J. Med. Chem.* **37**, 563, 1994); Dolle (*J. Med. Chem.* **38**, 220, 1995); Dolle (*J. Med. Chem.* **37**, 3863, 1994)]. As is evident, a minor structural change can lead to more than a 10-fold reduction in activity. Clearly, one cannot predict ICE inhibitory capability merely by looking at the structure of a compound. Moreover, the *in vitro* experiments were not done under identical conditions in the instant application as compared with the experiments done by Ku. Accordingly, attempting to extrapolate from the *in vitro* data disclosed in this application to the therapeutic results obtained by Ku leads to "unpredictable" results.

Consider also the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNF $\alpha$  and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL-1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.
- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an antiinflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).
- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.
- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF- $\beta$  was effective to inhibit IL-1 $\beta$  production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF- $\beta$ . The IL-1 $\beta$  production was not inhibited if the TGF- $\beta$  was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1 $\beta$  when used prior to stimulation of cells (which stimulation produces the IL-1 $\beta$ ), attempting to inhibit production of IL-1 $\beta$  by using agent "X" after stimulation of the cells leads to "unpredictable" results.
- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of human disease leads to "unpredictable" results. It is suggested that the existing method claims be cancelled. One option would be to add method claims which are similar to those allowed in parent application 09/430822 (now USP 5,420,522).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



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